SYSTEMIC REACTIONS TO TOPICALLY APPLIED DRUGS*

Howard Fox Memorial Lecture

FRANCES PASCHER, M.D.

Professor Emeritus of Clinical Dermatology
New York University School of Medicine
New York, N. Y.

Clinical Professor of Dermatology
University of North Carolina School of Medicine
Chapel Hill, N. C.

THIS is an especially exciting occasion for me. To me Howard Fox is more than a legendary or impersonal historical figure. I had the privilege of being interviewed by him in 1933, when I submitted my first paper for publication to the then *Archives of Dermatology and Syphilology*. Dr. Fox called me to his office to discuss the paper, and I can attest to the fact that what is claimed is true: namely, that he read every word of the 3,003 papers submitted to the *Archives* during his editorship. I am also aware of the honor conferred upon me by your chairman and selections committee in inviting me to give the Twelfth Howard Fox Memorial Lecture, thereby ushering in the centennial year of his birth.

Howard Fox was born in London, where his parents were living temporarily. His illustrious father, George Henry Fox, noted the event in his autobiography as follows:

> The Fourth of July, 1873, we celebrated in a somewhat unusual manner. I cannot recall exactly what I did in honor of the day but remember with vivid distinctness the interesting circumstance that on that National holiday in a foreign land my wife presented me with a son and heir. Of course, he can never be president of the United States, but there are still other fields of usefulness in which the U.S. Constitution did not at that time hinder his efforts to achieve success.[1]

And indeed Howard did achieve success: as scholar, teacher, editor,

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author of 120 medical articles, and contributor to and author of a number of medical textbooks. He is also credited with having been the first in the country to perform the original Wassermann test, the first to study cutaneous disease in blacks, and the first to become expert in tropical diseases.

Howard Fox's quality of leadership becomes evident in the positions he held, of which I shall mention but a few: first chairman of the Section on Dermatology of the New York State Medical Society, first president of the American Board of Dermatology, first president of the American Academy of Dermatology, chairman from 1921 to 1923 of the Section on Dermatology and Syphilology of the New York Academy of Medicine, and chairman from 1925 to 1938 of the Department of Dermatology and Syphilology of the New York University School of Medicine. We are memorializing one of the deans of American dermatology.[2]

Systemic Reactions to Topically Applied Drugs

My discussion will deal only with the systemic reactions that are attributable to the pharmacologic and toxicologic effects of topically applied medications.

That sufficient quantities of drugs may be absorbed from the cutaneous surface to cause systemic reactions is not generally recognized. It is of historic interest that, until the turn of the century, the skin apparently was regarded as being effectively impermeable except perhaps to gases. The properties of skin as a membrane have since been analyzed, and the laws of physics relating to the penetration of applied substances have been elaborated.[3, 4] In order that we may have a better understanding of how, why, and under what circumstances systemic reactions are more likely to occur, I shall discuss certain aspects of percutaneous absorption and especially examine some of the factors that may enhance the permeability of the skin for drugs.

Two principal pathways of penetration through the epidermis are recognized:[5] 1) the transappendageal route via the pilosebaceous units and sweat ducts, and 2) the transepidermal route via the stratum corneum (horny layer) between the appendages.

Under certain conditions and at different times either of these avenues may be the principal one. In general, shortly after the application of a topical agent, absorption is potentially far greater via the appendages than through the stratum corneum. After this initial period

of transappendageal absorption and perhaps from the outset for some molecules, the dominant mode of diffusion is through the stratum corneum, which provides a surface area approximately 10 times that of the total cross-sectional area of the pilosebaceous follicles in any portion of skin.[5]

For the purpose of our discussion we can think of the skin as made up of three distinct layers: the metabolically inert stratum corneum, the viable epidermis beneath it, and the dermis below. The most superficial layer, the stratum corneum, is the major barrier to the free diffusion of substance from without and to the loss of water from within. This keratinous zone varies considerably in thickness, from approximately 10 to 30 micra, depending on the anatomical location.

Electron microscopy discloses layers of keratinocytes: flat, platelike, cornified cells with thickened membranous walls separated by sparse intercellular substance.[6] Cells and cell walls are composed principally of filamentous proteins and lipids. It is suggested that water-soluble substances diffuse transcellularly through the water-holding, protein-rich filaments, while lipid substances penetrate the lipid-rich regions of the matrix. The relative impermeability of human skin compared to other mammalian biologic membranes is attributed to the apparent absence of specialized transport systems for cells of the stratum corneum. The structure and function of these cells are such as to make it a passive diffusion medium.[4] Whether a second barrier, situated at the dermal-epidermal junction, exists for some compounds is controversial. The consensus is that for most if not all substances the superficial barrier is the critical one. To quote Malkinson:[7] "Once it has been breached further passage into the epidermis, corium and capillaries is virtually assured." Having traversed the capillary walls, drugs then enter the systemic circulation.

The factors that promote percutaneous absorption of potentially toxic drugs may be considered topically as follows: the physical state of the stratum corneum, environmental conditions, and the drug and how it is used.

The Physical State of the Stratum Corneum

The physical state of the epidermal barrier may be altered in a number of ways. According to Scheuplein, absence or removal by stripping has been shown to result in an abrupt increase in permeability,

as much as 1,000-fold.[8] Not unexpectedly, then, impairment of keratinization or disruption of the barrier layer such as occurs in a wide variety of disorders and, in burns, will result in greatly diminished barrier function.

Age likewise may play a role. The high ratio in infancy and childhood of toxic effects and intensified reactions to topical drugs may be attributable at least partly to enhanced percutaneous absorption. This is not to lose sight of the fact that, as with oral and parenteral drugs, immaturity in enzymatic mechanisms for detoxification and excretion of drugs may likewise be contributory.

Individual variation with respect to absorption is bound to occur as with other physiologic phenomena. For example, in a comparative study of the percutaneous absorption of corticosteroids from the normal skin of matched subjects, McKenzie and Stoughton[9] showed that under identical conditions there was considerable variation among test subjects in the degree of vasoconstriction elicited. They assumed the variability was due to individual differences in percutaneous absorption. In addition, however, one should consider the likelihood of some variability in the vascular response also.

Environmental Conditions

In 1961 Sulzberger and Witten[10] demonstrated that the therapeutic effectiveness of hydrocortisone was markedly increased when the site of application was covered with plastic film. This important clinical observation was soon confirmed by laboratory studies showing that the percutaneous absorption of topical corticosteroids may be increased as much as 100-fold by the use of an occlusive polyethylene dressing such as Saran Wrap. Hydration by trapped perspiration and a local increase in the temperature explain the phenomenon.[9] That the absorption of drugs may be enhanced by warm and humid climatic conditions has likewise been demonstrated.[11] Further, small doses of ultraviolet light or grenz rays may have a similar effect, presumably because of damage to epidermal cells.[12]

The Drug and How It Is Used

In general one may say that the development of baneful systemic effects following the topical application of a potentially toxic drug depends upon the concentration, the number of applications in 24 hours, the duration of exposure, and the size of the surface area treated. It is

well to remember that total body treatment of the average adult may mean 18,500 sq. cm. of permeability.

The vehicle also may be significant. Stoughton finds that corticosteroid ointments utilizing the identical steroid are more biologically active than creams or lotions. He attributes this to the relative occlusiveness of ointments.[13] Further, the importance of the release of the active principle from the vehicle upon application to the skin has been emphasized for corticosteroid formulations.[14]

Now let us see how these considerations apply to the drugs we are about to discuss.

Topical Corticosteroids

Whether topical corticosteroids can induce systemic reactions is of the utmost significance, since these drugs are now used so extensively in the management of dermatologic disorders. To enhance their potency they are frequently applied under occlusion; in erythroderma or widespread psoriasis the entire body may be enveloped by occlusive wraps.

Two facts are no longer questioned. First: corticoids are absorbed percutaneously[15] and, second, at least one fluorinated corticosteroid, 9-alpha flurohydrocortisone, can be absorbed in sufficient quantities to cause Cushingoid side-effects.[16, 17] Topical fludrocortisone, with the exception of two ophthalmic and an otic preparation (Florinef-S and Florotic-Squibb), has been withdrawn for this reason. What is disputed is whether the topical use of hydrocortisone or any of the available fluorinated corticosteroids can suppress pituitary-adrenal function, resulting in secondary insufficiency and in the impairment of the body's ability to cope with stress. Most clinical and laboratory studies designed to answer this important question deal with the fluorinated preparations, a few with hydrocortisone.[18-21] The observations have been made chiefly in adults and are based on use of the fluorinated corticosteroids for an average of seven to 14 days. The outcome of 17 studies was as follows: no evidence of adrenal suppression or diminished reserve could be demonstrated in five,[22-26] the effect was equivocal in a sixth[27] while, in 11 studies, investigators found either reduced plasma cortisol levels or reduced concentrations of urinary 17 hydroxycorticoids or 17 ketosteroids. While the response to metyrapone or corticotropin was diminished in some patients, it was not in others.[28-38] The disparity in the results can be explained by the lack of uniformity in the total area

treated, the presence or absence of occlusion, the number of hours of occlusion, the number of applications in 24 hours, the amount applied, the nature of the dermatosis treated and, finally, in the criteria used to assess suppression or insufficiency. Further analysis of these studies shows that of all the variables mentioned, total body inunction and occlusion appeared to be the major factors in causing suppression. This applies to all the fluorinated corticosteroids now in use, since each was evaluated in one study or another. Surprisingly small amounts, at times as little as 22.5 gm. of 0.1% triamcinolone acetonide cream under occlusion daily, was sufficient to induce suppression in a generalized dermatitis.[36] In the main, however, about 45 gm. a day of any of the standard-potency creams was required. Diluted preparations (0.01% triamcinolone acetonide and 0.01% fluocinolone acetonide) were found to have the same effect.[31, 33, 34] In one of their patients Scoggins and Kliman[33] found that the suppressive effect of 40 mg. triamcinolone acetonide (40 gm. of 0.1% cream) twice daily under occlusion was about the same as eight to 32 of triamcinolone a day orally. The consensus is that the diminished secretion of endogenous cortical steroids is transient, and that once topical applications are stopped the adrenals recover within 48 hours. The clinical significance of these studies has been questioned by many because of the seeming absence of systemic side-effects, despite extensive and long-term use. This no longer holds true for adults, nor has it been true for children. At a recent meeting of the American Academy of Dermatology, Wallace[39] reported two deaths associated with the prolonged topical use of fluorinated corticosteroids. One adult with generalized striae experienced an Addisonian crisis; the other died of septicemia following an infection that developed under occlusion.

There are also a number of disturbing reports of untoward systemic effects in children. The case histories, in summary, are as follows. A three-week-old infant with epidermolysis bullosa developed Cushingoid features and edema while under treatment with ¼% HC lotion. In the course of 10 days approximately 300 mg. of the drug had been administered.[40] A patient of Fanconi, an infant treated with 1% HC ointment twice daily over a period of three months for generalized eczema, developed arrest of growth. Growth resumed after treatment was stopped.[41] A third patient, a five-and-a-half-year-old boy with chronic eczema, had been treated with 1% HC alcohol ointment for 16 months.

In addition to an accelerated increase in weight, together with retardation of growth, the boy developed benign intracranial hypertension (pseudotumor cerebri), a well-documented complication of the withdrawal of systemic corticosteroid.[42, 43] The authors reasoned that the concurrent reduction in the absorption of the steroid with the healing of the eczema was not unlike systemic withdrawal. Finally Feiwel and his coinvestigators found an appreciable lowering of plasma cortisol levels in three infants of a group of 19 treated for eczema with 0.1% betamethasone valerate over a period of 21 to 18 months. They also noted that one of the infants failed to thrive.[38]

Phenol and Phenolic Derivatives

Fatal poisoning following the local application of phenol is, fortunately, a thing of the past. Insofar as I could determine, the last recorded death from the use of this substance was in 1949.[44] The patient was a 10-year-old boy who was treated for a kerosene burn with a preparation called Foille, composed of 2.36% phenol, together with traces of a number of other chemicals, in corn oil. With this case in mind, a plea is hereby made for the banning of all nonprescription items containing phenol. Mouthwashes and lozenges with 1 to 2% phenol, antifungal remedies with 5% phenol, and a number of items with unstated quantities of the drug are still purchasable over the counter.

Resorcinol

Resorcinol closely resembles phenol in its absorption and toxicity. The most recent account deals with two cases of resorcinol toxicity, both in young adults with pustular acne.[45] A peeling paste containing 40% of the drug was applied daily to the affected areas and was left on for one to four hours. This procedure was continued for a period of 33 days in one case and 22 days in the other when an application was followed by a striking reaction: dizziness, pallor, cold sweat, tremors, collapse, and violet-black urine. Happily, these patients recovered. That resorcinol, even in low concentrations, should not be prescribed for infants and young children because of the deaths attributed to its absorption is a rule that must ever by borne in mind.[46]

Salicylic Acid

Salicylic acid, another phenolic derivative, merits discussion for a

number of reasons. First, by virtue of its keratolytic effect in concentrations of three or more per cent, this drug may enhance the absorption of other medicaments used concurrently or sequentially. Second, when salicylic acid is added to ammoniated mercury, a not uncommon combination, the acidity contributed by the salicylic acid hastens the slow dissociation of mercuric ions, normally dependent upon the acid reaction of the horny layer and sweat.[47] Mercuric chloride, formed in this way, is absorbed more readily than the ammoniated form: the consequences of this will be discussed later. Third, reports of mild-to-fatal poisoning from the percutaneous absorption of salicylic acid itself are by no means rare. In 1964 von Weiss and Lever[48] reviewed the recorded fatalities. Ten of the 13 were in children. Five had been treated for scabies, three for some form of dermatitis, one for lupus vulgaris, and one for congenital icthyosiform erythroderma. The most dramatic account is that of two plantation workers in Bougainville, in the Solomon Islands, who were painted twice in one day with an alcoholic solution of 20.0% salicylic acid for tinea imbricata involving about 50% of the body. The victims were comatose within six hours and dead within 28 hours. No other cause of death was disclosed at postmortem examinations.[49]

Most instances of salicylism have been in children with ichthyosis congenita and in adults with generalized psoriasis.[48, 50, 51] Concentrations of 3 to 6% salicylic acid in ointment form were applied six times daily for the psoriasis.[48] Early signs of toxicity in children are deep and rapid breathing, adults are more likely to complain of ringing in the ears, dizziness, or impaired hearing. Purpura, or scarlatiniform eruption, may bring the patient to the dermatologist. Nausea, vomiting, and abdominal cramps may also be among the early symptoms.

A more severe degree of salicylate intoxication is marked by alterations in the acid-base balance and involvement of the central nervous system. The mental disturbances, sometimes referred to as a "salicylate jag," simulate alcoholic inebriation. To quote Goodman and Gilman, "euphoria and elation are absent, however, and the experience is rather a melancholy affair."[52]

Hexachlorophene

Hexachlorophene (HCP), a chlorinated bisphenol, continues to make headlines.[53] As of November 1972 the total number of deaths

attributed to the topical use of 3% solutions reached 15 in this country. There were nine cases of burns among them, seven in children, and two in adults. A blood level of 2.2 μg./ml. of HCP was cited for one of these fatalities.[54] Two neonates with congenital ichthyosis were also among the cases, which brings the number of deaths of dermatologic import to 11/15. Prolonged seizures, disorientation, bizarre behavior, and coma were among the symptoms heralding demise.

It has taken 20 years to learn that HCP is not an innocuous drug, that it is absorbed from intact as well as denuded skin, and that not all cases of poisoning are due to its accidental ingestion. The earliest known death following its topical use occurred in 1954; the patient was a seven-month-old premature infant with a rash who had been bathed with pHisoHex.[53] Herter in 1959 described a second case of severe poisoning.[55] Three per cent HCP lotion for the care of a neonate was continued by the mother at home after the infant was discharged from the hospital. The medication was not washed off at any time. Diffuse redness and widely scattered excoriations appeared within a few days. This was soon followed by twitchings and convulsions. The baby was readmitted on the 11th day when a roving nystagmus and paralysis of the left side of the body were noted. Fortunately, most of the symptoms cleared within a few days after the drug was discontinued. Blood levels of HCP were not determined in this case.

Larson's informed guess in 1968[56] that the syndrome known as "burn encephalopathy" could be due to absorption of HCP led to his investigation of the serum and cerebrospinal fluid HCP levels of patients subjected to various treatments with this agent at the Shriner's Burn Institute, in Galveston, Texas. High concentrations of HCP were found. I shall not burden you with the figures since the methods used appear to be different from those now in use for quantitative determinations of HCP.[54]

Prospective studies of HCP in animals and man followed. I shall speak only of the one conducted by Curley and his coinvestigators on the dermal absorption of HCP in infants because of its relevance to my topic.[57] Fifty healthy newborn infants were washed daily for 11 days with diluted HCP solution. Rinsing was avoided, in order to permit a film of detergent solution to remain on the skin. The mean HCP concentration at birth in whole cord blood was 0.022 μg./ml. (the range 0.003 to 0.182 μg./ml. At the time of discharge from the hospital the

mean value was approximately five times higher, 0.109μg./ml. (the range 0.009 to 0.646 μg./ml.) However, these infants did not manifest any toxicity. Conceding the possibility of some oral contamination and ingestion of HCP, the authors nevertheless concluded that most of the drug had been absorbed through the skin.

Moreover, studies conducted in volunteers simulating "normal" use of HCP have shown that absorption from various products depends on the concentration of the drug, the method used, the frequency and duration of exposure, and the percentage of body surface exposed.[54] Suffice it to say that mean blood values up to 1.08 μg./ml. of HCP were obtained in this manner.[54] From the information at hand it is difficult to interpret these levels. What is important is the fact that measurable quantities can be absorbed from intact skin and lethal quantities from damaged skin. All of this has culminated in the present regulations of the Food and Drug Administration with regard to the HCP content of drugs and cosmetics. Henceforth formulations containing more than 0.1% HCP will be obtainable by prescription only. Products containing less than 0.75% of the drug may be dispensed as nonprescription items but may not be replaced until the supply on hand is exhausted. Medicaments and cosmetics in which no more than 0.1% HCP is used as part of a preservative system remain freely available.

Boric Acid

We may now leave the phenols and turn our attention to boric acid. This clinically ineffective but potentially hazardous drug is still available. It is listed in the current *National Formulary* and *U.S. Pharmacopeia.* It is present in undeclared concentrations in any number of nonprescription items. Valdes-Dapena and Arey,[58] in reviewing the literature on boric-acid poisoning, found, interestingly, that almost one third of the patients, 53 of 172, had been treated externally. Twenty-three of the 53 died. It is perhaps symbolic that the principal source of native boron was for a time Death Valley, Calif.

A case typifying boric-acid intoxication following topical use appeared in the *Archives of Dermatology* a few years ago.[59] A dusting powder, advertised as "safe for baby's sensitive skin," was applied several times daily to a three-year-old boy with diaper rash. After three months symptoms of toxicity appeared. Edema of the lids and desquamation reminiscent of toxic epidermal necrolysis appeared in the axillary areas.

Flaccid bullae and exfoliation were also present in the suprapubic area and along the inner aspect of the thighs. The "boiled lobster" or scarlatiniform appearance of the skin that is associated with boric-acid toxicity is more typical of acute poisoning. This child was also febrile, restless, and irritable. The diagnosis of borism in this case was confirmed by the finding of high levels of baron acid in the blood (5.4 mg.% as compared to a norm of 0.08 mg.%).

Mercurials

Mercury poisoning is perhaps the most familiar chapter in topical toxicology, dating back to the 1500s, when mercurial inunctions were first used in the treatment of syphilis. I wonder how many of us here know the origin of the expression "mad as a hatter" in Lewis Carroll's *Alice in Wonderland*. It was generally known that felt-hat workers exposed to mercuric nitrate in the course of their occupation developed many of the classic symptoms of chronic mercurial poisoning. These are extreme instability, psychotic symptoms of a schizoid nature, erythematous skin lesions, chronic stomatitis, ptyalism, diarrhea, and abdominal pain.

Two other notable adverse effects are linked with the topical use of mercury: acrodynia (pink disease),[60, 61] seen in infants and young children; and nephrotic syndrome of adults.[62, 63] Anyone faced with the prospect of "board exams" may be inspired by the fact that it was Warkany, while reviewing pharmacology in preparation for the Ohio State Medical Board Examinations, who first thought of looking for mercury in the urine of patients with acrodynia.[64] This disorder still exists, but it is extremely rare.[65] Because of severe photophobia these patients often take the prone position with head buried in the pillow, eyelids held tightly shut. They may cry out because of excruciating pain in the hands and feet. The polyneuropathy is usually accompanied by redness and swelling of the distal portion of the extremities. Erythema and desquamation may be generalized in some instances. Other signs and symptoms are irritability, restlessness, profuse sweating, tachycardia, hypertension, and elevated levels of mercury in the urine (>5 to 25 μg./24 hours, dithizone method).

Approximately 17 cases of proteinuria have been reported in the past 15 years. The low prevalence, which may reflect underreporting or a lack of testing, is in sharp contrast to the outcome of Young's prospec-

tive study.[66] Young found that in a group of 70 psoriatics treated with daily applications of 10% ammoniated mercury ointment to the scalp, one sixth, or 15%, developed proteinuria among other symptoms of general toxicity within six weeks. Nine cleared rapidly after the treatment was discontinued; in two, the albuminuria was more prolonged.

Podophyllum Resin

Podophyllum resin has been selected for comment, not only because of the recorded adverse systemic effects attending its topical use but because of the development in recent years of a number of other antimitotic drugs (nitrogen mustard, fluorouracil, and hydroxyurea) which are applied locally for benign and malignant proliferative processes. The experience with podophyllum resin should alert us to the possibility of systemic absorption of these newer antiproliferative agents.

One death and four cases of nonfatal intoxication with podophyllin have been gleaned from the literature.[67-70] In each instance the systemic reaction was associated with a severe local reaction. The fatality occurred in an 18-year-old pregnant woman who was treated with 25% podophyllin ointment for condyloma acuminata covering the perineum.[68] Enhanced absorption because of the unusual extent of the infection, the nature of the vehicle, and failure to remove the preparation within a few hours contributed to the fatal outcome.

I have by no means exhausted the list of topical drugs that may be attended by systemic effects. I want to emphasize the following points:

Topical drugs can elicit untoward systemic effects.

Adverse reactions occur more readily in infants and young children. The likelihood in adults is also greater when potentially toxic drugs are applied to extensive areas for prolonged periods, especially when occlusive or semiocclusive dressings are used.

When potent topical agents are administered, thought must be given to the concentration, amount, frequency, and technique of application.

Although the reactions described are uncommon, it is necessary to be thoroughly familiar with the manner in which they come about.

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